



# Optimum adjuvant trastuzumab duration for human epidermal growth factor receptor-2 positive breast cancer: a network meta-analysis of randomized trials

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**Background:** Adjuvant trastuzumab treatment for 12 months is the standard-of-care for early HER2-positive breast cancer; however, the optimal duration is unclear. We performed a network meta-analysis (NMA) to determine the optimal treatment duration.

**Methods:** We identified 16 randomized controlled trials involving 29,837 patients that assessed trastuzumab treatment in HER2-positive early breast cancer. Our NMA compared six trastuzumab durations: observation, T-9 weeks, T-12 weeks, T-6 months, T-12 months, and T-24 months. We assessed overall survival (OS), disease-free survival (DFS), acceptability, and cardiotoxicities and grade 3–4 nonhematologic toxicities, and ranked the durations in terms of efficacy and safety by surface under the cumulative ranking (SUCRA).

**Results:** Pairwise meta-analysis showed that while T-6 months was associated with a significant reduction in DFS compared to T-12 months. In our NMA, increasing or decreasing durations showed a significant benefit in DFS compared to observation; however, decreasing durations was not associated with a significant reduction in DFS compared with T-12 months, regardless of the lymph node and hormone receptor statuses. SUCRA ordered the optimum durations of trastuzumab treatment based on PFS as T-12 months (95.6%), T-24 months (69.6%), T-6 months (53.2%), T-9 weeks (41.2%), T-12 weeks (34.3%) and observation (6.1%).

**Conclusions:** Escalating trastuzumab treatment beyond T-12 months confers no additional survival benefit but increased risk of cardiotoxicities. Furthermore, de-escalating treatment confers no improvement on OS compared to T-12 months. These data suggest that T-12 months is the most appropriate treatment schedule for HER2-positive early breast cancer.

**Keywords:** Early breast cancer; trastuzumab; network meta-analysis (NMA)

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## Introduction

Human epidermal growth factor receptor-2 (HER2)-

positive breast cancer accounts for ~20–25% of all breast cancers (1,2) and the overall prognosis of HER2-positive breast cancer is poor compared to other breast cancer

subtype (3). Trastuzumab is a monoclonal antibody which specifically targets the extracellular domain of HER2 (4). Several pivotal phase III clinical trials have proved that a 12-month (T-12) treatment duration is superior to observation (4-7), leading to national and international guidelines to recommend T-12 months treatment with or after chemotherapy as the standard-of-care (8-10). A shorter duration of trastuzumab is associated with reduced side effects and costs (11), the optimum duration of trastuzumab treatment may be hampered by efficacy, toxicity, convenience, and cost (12).

High-quality randomized controlled trials (RCTs) have aimed to evaluate the optimum duration of trastuzumab treatment (3-6,12). For example, the HERA trial showed that trastuzumab treatment for 24 months (T-24 months) did not improve disease-free survival (DFS) compared to treatment for T-12 months [hazard ratio (HR) 1.02, 95% confidence interval (CI): 0.89–1.17], and was associated with higher costs, inconvenience, and cardiac toxicity (7.3% *vs.* 4.4%) (12). The PERSEPHONE trial compared T-12 months trastuzumab treatment with 6 months (T-6 months) treatment, and found that T-12 months was non-inferior and decreased cardiac toxicity (8% *vs.* 4%,  $P < 0.001$ ) (13). Conversely, the PHARE and HORG trials failed to show that T-12 months was non-inferior compared to T-6 months (14-16). Finally, the SOLD and Short-HER trials found that trastuzumab treatment for just 9 weeks (T-9 weeks) was inferior to T-12 months, but conferred fewer cardiac adverse effects (17,18). Together with these conflicting results, a considerable gap exists in the current literature as a large proportion of the RCTs have compared active therapy to inactive interventions (e.g., observation) (5,6,12) rather than comparing different treatment durations. De-escalating trastuzumab treatment in HER2-positive early breast cancer has attracted the attention of many investigators (9). Previous studies also showed that T12-month trastuzumab treatment prevents disease recurrence and confers survival benefits for patients with HER2-positive early breast cancer compared with observation (19). Five important systematic reviews attempted to resolve the debate over de-escalating treatment and standard care, and the results undoubtedly concluded that T-6 months could not replace T-12 months in patients with HER2-positive early breast cancer based on inferior survival (12,14-17). However, these studies failed to make sufficient comparisons between de-escalating treatments and standard care in terms of survival and toxicities to draw firm conclusions. Finally, there is no information

on de-escalating and escalating trastuzumab treatment in patients with HER2-positive early breast cancer; thus, there is heated controversy about whether escalating and de-escalating treatment might be considered a new standard of care.

This study used a network meta-analysis (NMA) approach (18) to evaluate multiple interventions in a single analysis and the clinical outcomes as a result of escalating, de-escalating and standard (T-12 months) trastuzumab treatments. Specifically, we synthesized all available evidence from 16 RCTs based on the direct and indirect comparisons of trastuzumab efficacy and safety to identify the optimum treatment duration (T-24 months *vs.* T-12 months *vs.* T-6 months *vs.* T-12 weeks *vs.* T-9 weeks *vs.* observation) with the greatest clinical value in HER2-positive, early breast cancers. This study was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist (20,21) (available at <http://dx.doi.org/10.21037/tcr-20-2378>).

## Methods

A detailed protocol has been registered in PROSPERO (CRD42019139109) and published in BMJ Open recently (22).

### Search strategy

Titles and abstracts referring to trastuzumab treatment for early breast cancers were searched in the electronic PubMed, Cochrane Library and Embase (Ovid interface) databases from conception to June 16, 2019. Titles and abstracts were also searched in international meeting proceedings, including the San Antonio Breast Cancer Symposium (SABCS) (2015 to 2019), European Society of Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO).

Two reviewers trained in data extraction conducted the searches, independently. Pairs of reviewers then manually searched the reference lists from eligible reviews and relevant RCTs to identify additional potential studies for inclusion. The reasons for excluding a full-text article were recorded and a PRISMA flow diagram for the NMA was generated.

The search terms included the following domains of the Medical Subject Heading (MeSH) terms: ‘breast cancer’, ‘human epidermal growth factor receptor-2’ and ‘trastuzumab’, according to the Population Intervention Comparison Outcomes Study Design (PICOS) statement.

These MeSHs and subheadings were combined with 'AND' or 'OR'.

A pilot test was performed to evaluate inter-rater reliability and to adjust each screening stage: title and abstract, followed by full-text screening. Then, independent reviewers screened the titles and abstracts of related RCTs studies based on the inclusion and exclusion criteria (see below). The eligible or potentially eligible trials were assessed by reading the full texts when necessary. Any disagreements over data extraction were resolved by discussion or the other reviewer.

### *Data extraction and management*

Literature search records were maintained in EndNote X7 (Thomson Reuters, CA, USA). Microsoft Excel 2010 (Microsoft Corp, Redmond, WA, [www.microsoft.com](http://www.microsoft.com)) was used to collect outcomes of interest, including the first author, study design, recruitment time frame, interventions, sample size, and study endpoints (OS, DFS, acceptability, and cardiac and grade 3–4 nonhematologic toxicities).

### *Inclusion criteria*

Trials were eligible if they met the following criteria: (I) population: HER2-positive early breast cancer patients of any age or ethnicity, treated with trastuzumab; (II) Interventions and Comparators: any duration of trastuzumab treatment; (III) outcomes: OS, DFS, acceptability, and cardiotoxicities and grade 3–4 nonhematologic toxicities; (IV) study design: RCTs; (V) language and other limitations: studies published in English language without date limitations. There were no restrictions on patient performance status (PS), or nationality.

RCTs involving interventions using trastuzumab biosimilars or combined palliative care with trastuzumab were excluded. Reviews, posters, abstracts, editorials and case reports, retrospective and prospective cohort studies were also excluded.

### *Outcomes*

The study outcomes were OS, DFS, acceptability, and cardiac and grade 3–4 nonhematologic toxicities. The Common Terminology Criteria for Adverse Events of the National Cancer Institute was used for cardiac toxicity grading. Cardiac toxicity was defined as an asymptomatic decline in the left ventricular ejection fraction (LVEF)

to  $\leq 45\%$ , an absolute drop of 10–15% in follow-up echocardiography, symptomatic congestive heart failure [New York Heart Association (NYHA) class III/IV] or cardiac death (23,24). The relative effectiveness for each network comparison was calculated among all interventions as previously described (25,26).

### *Risk of bias*

The risk of bias of RCTs in the NMA was assessed using the following domains outlined by the Cochrane Collaboration (27): random sequence generation, allocation concealment, participant and personnel blinding, incomplete outcome data, selective outcome reporting, and other bias. Two authors independently reviewed the RCTs and reported a high risk of bias as “–”, a low risk of bias as “+”, or an unclear risk of bias “?”. Any disagreements on the risk of bias were resolved by discussion or the third reviewer, if needed.

### *Quality of evidence*

The quality of evidence produced by the NMA was assessed using a modified version of the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) (28). The GRADE process was completed using GRADEprofiler software (version 3.6.1) with the following primary domains: risk of bias, imprecision, inconsistency, indirectness and publication bias (29). The GRADE evidence was then categorized into the following stages: (I) high, (II) moderate, (III) low and (IV) very low quality. The starting confidence level for each network estimate was high but decreased according to the evaluation of the primary domains. Any disagreements were resolved by discussion between the two reviewers, with the help of a third reviewer.

### *Statistical analysis*

Traditional pairwise and NMA were performed, and all graphics for pairwise analyses and NMA were generated with Stata 13.0 (StataCorp, College Station, TX, USA) (30). To cross-compare all eligible interventions, NMAs for the outcomes of interest were conducted according to a Bayesian Markov chain Monte Carlo approach, as previously described (31), in WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK). Results regarding OS and DFS were calculated as HRs with 95% CIs. Kaplan-Meier curves were extracted using Getdata Graph Digitizer

2.26 ([www.getdata-graph-digitizer.com](http://www.getdata-graph-digitizer.com)) and were calculated via summary statistics where necessary, as previously described (32). The WinBUGS code was described by Woods and his colleagues (33). Each posterior distribution of the model parameter was calculated by generating 10,000 iterations with a 5,000 burn-in and a thinning interval of 1 for each chain.

A loop-specific method was used to statistically evaluate inconsistencies between the direct and indirect comparisons (34). Both fixed-effects and random-effects models were run. Inconsistencies were assessed by comparing the deviation information criteria (DIC) statistics in the fitted consistency and inconsistency models (35). The convergence of the model was assessed by the potential scale reduction factor (PSRF), where PSRF closer to one indicated the better convergence (36). The results of the probability statements of the intervention effects were ranked using surface under the cumulative ranking (SUCRA).

The most effective interventions in terms of efficacy and safety were then further evaluated to interpret the relative effect of all comparisons. Risk-benefit analyses for efficacy and toxicity in each pairwise comparison was completed. A two-sided  $P < 0.05$  was considered statistically significant. The degree of heterogeneity was estimated based on the magnitude of  $I^2$ , which derived from the NMA models:  $I^2 > 50\%$  supported high heterogeneity (37). In cases of high heterogeneity, a random-effects model was used; otherwise, a fixed-effects model was used. Publication bias was explored using a funnel plot.

### Subgroup and sensitivity analyses

To explore whether particular breast cancer subtypes might be more or less appropriate for specific trastuzumab durations, breast cancers were stratified into the following groups: hormone receptor-positive, hormone receptor-negative, lymph node-positive and lymph node-negative. Subgroup analyses were conducted by pairwise comparisons and NMA, regardless of the heterogeneity estimates. Sensitivity analyses were conducted based on hormone receptor and lymph node statuses.

## Results

### Systematic literature review

We identified 1,500 records from our database searches; 385 were duplicates, and 1,044 were excluded for not

meeting the study criteria (see materials and methods) after screening the titles and abstracts. Of the remaining potential 71 full-text articles, 41 were excluded mostly because of the involvement of palliative care in the intervention ( $n=12$ ), trastuzumab-induced cardiotoxicity ( $n=7$ ), a pairwise meta-analysis was performed ( $n=5$ ), the study had a retrospective nature ( $n=4$ ) or for other reasons ( $n=13$ ). Ultimately, 30 articles corresponding to 16 RCTs met the criteria for inclusion in our review (4-7,13,19,38-54) (*Figure 1*).

### RCT characteristics

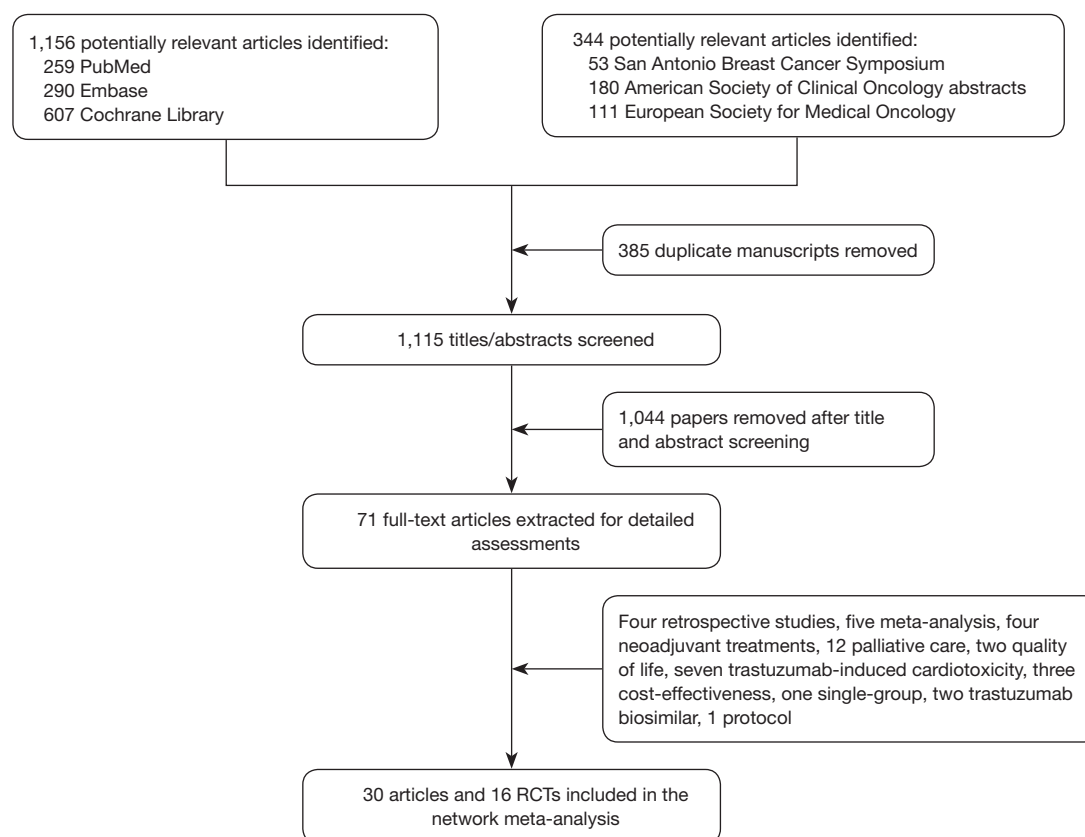
The 16 eligible RCTs included a total of 29,837 patients (*Table 1*). These RCTs were published between 2005 and 2019, and the number of patients ranged from 227 to 4,118 per trial. All RCTs were included in the survival analysis and were suitable to analyze congestive heart failure rates in the recruited patients. We used updated survival data to collect HRs for DFS and OS with 95% CIs in our NMA: HRs with 95% CIs were directly reported in 14 studies and could be estimated in two studies, but the remaining study did not provide an HR estimate for OS (NeoSphere).

### Network plot

We performed a network plot of six comparisons for the outcomes of interest (*Figure 2*): observation, T-9 weeks, T-12 weeks, T-6 months, T-12 months, and T-24 months. Patients were randomized to receive one of the previously mentioned treatment options. Two loop-specific with no inconsistencies were found in the NMA (*Figure S1*). Two RCTs had three arm-based studies and the remaining was two arm-based studies. The size of the node and the thickness of solid lines were directly proportional to the number of patients and the number of interventions, respectively. *Figure S2* showed that there were six mixed comparisons and eight indirect comparisons in our NMA (*Figure S2*).

### Risk of bias and quality assessment

All RCTs included in the NMA showed a low risk of bias in terms of the allocation concealment, random sequence generation and incomplete outcome data. Although these studies were open-label clinical trials, the results of interest were measured objectively in each trial and had a low risk of bias for blinding participants and personnel. The bias risk for all other sources was low in our NMA (*Figure S3*).



**Figure 1** Literature search and selection.

In addition, funnel plot analysis did not detect any notable publication bias (Figure S4).

Finally, we assessed the quality of the outcomes of interest according to the GRADE criteria (Table S1). For most of the interventions, the quality of the primary endpoints of interest was determined to be either moderate or high.

### Pairwise meta-analysis

All 16 RCTs included in our analysis reported information on DFS; only one trial did not report on OS. Here, we found that T-12 months was associated with a significant improvement in DFS compared to observation (HR 0.65, 95% CI: 0.59–0.70,  $I^2=20.5\%$ ). Conversely, T-6 months was associated with a significant reduction in DFS compared with T-12 months (HR 1.15, 95% CI: 1.01–1.28,  $I^2=21.0\%$ ). Although not significant, the DFS conferred by T-12 months treatment was longer than the DFS conferred by T-9 weeks treatment (HR 1.25, 95% CI: 1.00–1.50,

$I^2=38.3\%$ ) (Figure 3A). When comparing to observation, the OS data were consistent with the DFS data for T-12 months (HR 0.73, 95% CI: 0.66–0.79,  $I^2=5.0\%$ ). Neither T-6 months (HR 1.14, 95% CI: 0.98–1.29,  $I^2=0.0\%$ ) nor T-9 weeks (HR 1.20, 95% CI: 0.90–1.50,  $I^2=0.0\%$ ) significantly differed from T-12 months in terms of OS (Figure 3B). Importantly, the differences between the traditional pairwise meta-analysis and the NMA were small, and there was consistency between direct and indirect evidence based on the comparisons of the results.

### NMA

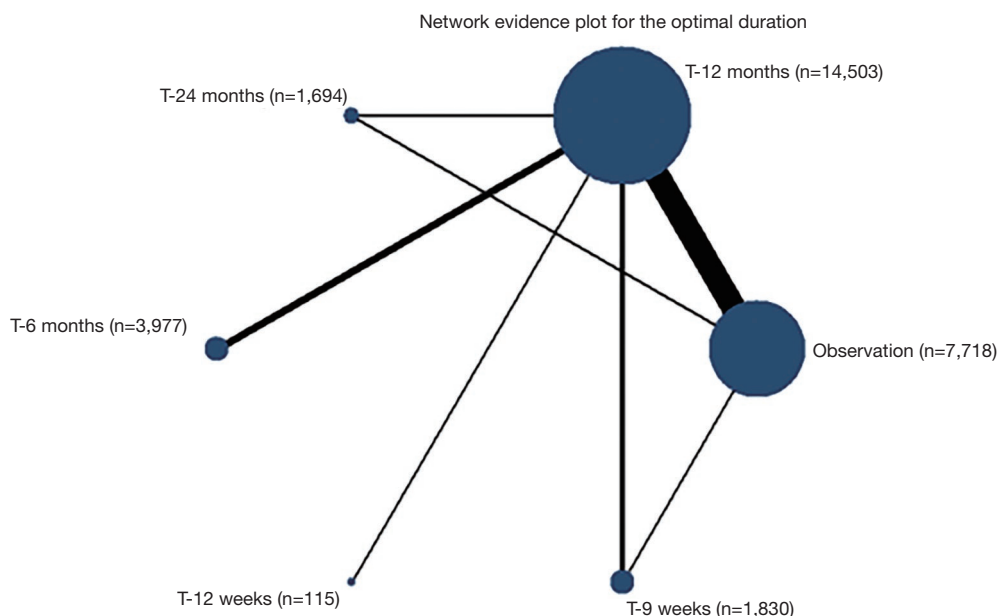
In our overall NMA, T-12 months, T-24 months, T-6 months, and T-9 weeks were all associated with significantly improved DFS compared to observation. Interestingly, no significant benefit was found between T-12 weeks and observation (HR 0.94, 95% CI: 0.76–1.17). When comparing to T-12 months, both T-6 months and T-9 weeks were associated with significantly improved DFS



**Table 1** Characteristics of the studies included in this NMA

Authors	Study identifier	N	Recruitment period	Primary endpoint	DFS HR (95% CI)	OS HR (95% CI)
Studies comparing 12 months to observation						
Slamon 2011	BCIRG 006	3,222	2001–2004	DFS	0.68 (0.56–0.83)* 0.81 (0.66–0.98) <sup>#</sup>	0.62 (0.48–0.79)* 0.81 (0.63–1.03) <sup>#</sup>
Perez 2011	N9831	2,184	2000–2005	DFS	0.69 (0.57–0.85)	0.88 (0.67–1.15)
Romond 2005	NSABP B-31	2,119	2000–2005	DFS	0.59 (0.50–0.68)	0.66 (0.54–0.79)
Martine 2005	HERA	1,694	2001–2005	DFS	0.54 (0.43–0.67)	0.76 (0.65–0.88)
Marc 2009	PACS 04	528	2001–2004	Efficacy & tolerance	0.86 (0.61–1.22)	1.27 (0.68–2.38)
Baselga 2012	NeoALTTO	306	2008–2010	PCR	0.75 (0.41–1.36) <sup>§</sup>	1.31 (0.62–2.80) <sup>§</sup>
Gianni 2016	NeoSphere	201	2007–2009	PCR	0.56 (0.22–1.40) <sup>§</sup>	NA
Gianni 2014	NOAH	235	2002–2005	EFS	0.64 (0.44–0.93)	0.66 (0.43–1.01)
Martine 2016	ALTTO	4,118	2007–2011	DFS	0.63 (0.52–0.75)	0.76 (0.56–1.02)
Studies comparing 24 months to observation						
Martine 2005	HERA	1,693	2001–2005	DFS	0.77 (0.69–0.87)	0.74 (0.63–0.86)
Studies comparing 9 weeks to observation						
Joensuu 2006	FinHer	232	2000–2003	RFS	0.42 (0.21–0.83)	0.41 (0.16–1.08)
Studies comparing 24 months to 12 months						
Martine 2005	HERA	1,694	2001–2006	DFS	0.99 (0.85–1.14)	1.05 (0.86–1.28)
Studies comparing 6 months to 12 months						
Earl 2019	PERSEPHONE	4,089	2007–2015	DFS	1.17 (0.93–1.24)	1.14 (0.95–1.37)
Pivot 2019	PHARE	3,384	2006–2010	DFS	1.08 (0.93–1.25)	1.13 (0.92–1.39)
Mavroudis 2015	HORG	481	2004–2012	DFS	1.57 (0.86–2.10)	1.45 (0.57–3.67)
Studies comparing 12 weeks to 12 months						
Schneider 2015	E2198	227	1999–2000	Safety	1.31 (0.79–2.12)	1.37 (0.74–2.54)
Studies comparing 9 weeks to 12 months						
Joensuu 2018	SOLD	2,176	2008–2014	DFS	1.39 (1.12–1.72)	1.36 (0.98–1.89)
Conte 2017	ShortHER	1,254	2007–2013	DFS & OS	1.13 (0.89–1.42)	1.07 (0.74–1.56)

\*, doxorubicin and cyclophosphamide, followed by docetaxel plus trastuzumab (AC-TH); <sup>#</sup>, docetaxel and carboplatin, given concurrently with trastuzumab, followed by trastuzumab (TCH); <sup>§</sup>, HRs were estimated from summary statistics with the method described by Tierney *et al*. N, number of patients; DFS, disease-free survival; OS, overall survival; HR, hazard ratio; PCR, pathological complete response; EFS, event-free survival; RFS, relapse-free survival; and NA, not applicable.



**Figure 2** Network plot of the six comparisons for the outcomes of interest. The size of the node and the thickness of solid lines are directly proportional to the number of patients and the number of interventions, respectively. T, trastuzumab.

(Figure 4A). We produced similar findings for OS, with the exception that only T-12 months (HR 0.87, 95% CI: 0.85–0.91) and T-24 months (HR 0.88, 95% CI: 0.84–0.93) were associated with a significantly improved OS over observation (Figure 4B).

HER2 status is very an important predictor for anti-HER2 treatment. Because only 120 HER2-positive patients remained after re-evaluating the HER2 status in the E2198 trial (46), we found no significant benefit for T-12 weeks versus observation in our sensitivity analysis (HR 0.78, 95% CI: 0.57–1.07).

### Subgroup and sensitivity analyses

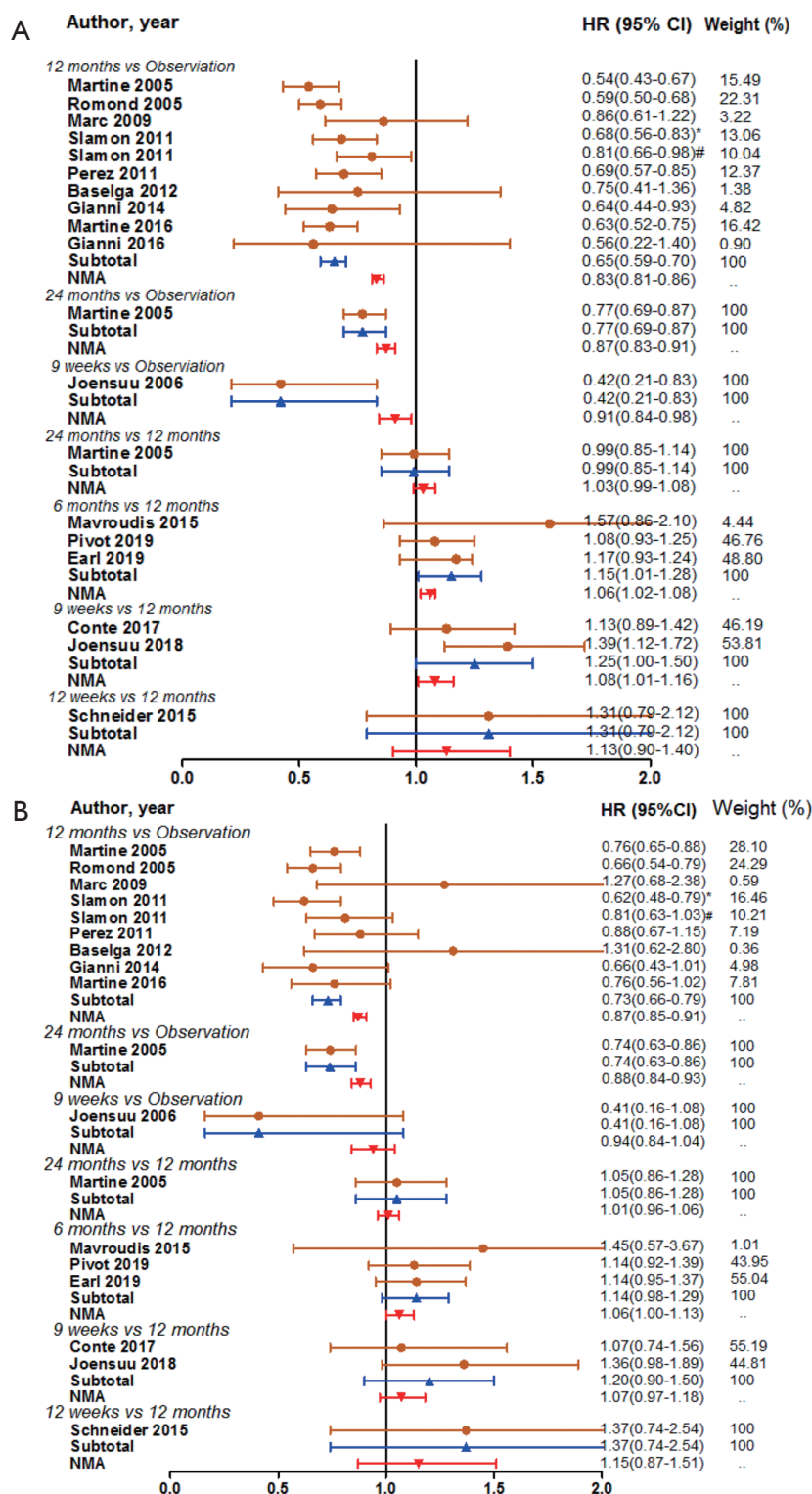
Subgroup analysis showed that regardless of lymph node status in early breast cancer, T-12 months was associated with significantly improved DFS compared with observation. Shorter treatments (T-6 months and T-9 weeks) were not associated with a reduced DFS compared with T-12 months in patients with node-positive (HR 1.09, 95% CI: 0.92–1.27,  $I^2=0.0\%$  and HR 1.24, 95% CI: 0.92–1.57,  $I^2=39.3\%$ , respectively) or node-negative (HR 1.11, 95% CI: 0.88–1.33,  $I^2=0.0\%$  and HR 1.01, 95% CI: 0.64–1.50,  $I^2=59.2\%$ , respectively) early breast cancer (Figure S5).

Next, we performed subgroup analyses for hormone receptor status. T-12 months and T-24 months were

associated with significantly improved DFS than observation in both hormone receptor-positive and hormone receptor-negative early breast cancers. As for hormone receptor status, shorter treatments (T-6 months and T-9 weeks) were not associated with a significant reduction in DFS in patients with hormone-positive (HR 1.03, 95% CI: 0.87–1.18,  $I^2=0.0\%$  and HR 1.23, 95% CI: 0.94–1.52,  $I^2=0.0\%$ , respectively) or hormone-negative (HR 1.15, 95% CI: 0.96–1.34,  $I^2=0.0\%$  and HR 1.35, 95% CI: 0.97–1.73,  $I^2=35.2\%$ , respectively) early breast cancer when compared with T-12 months (Figure S6).

Based on the subgroup analysis by indirect comparisons, T-12 months and T-6 months were associated with significantly improved DFS than observation for lymph node-positive early breast cancer. No such association was observed between T-9 weeks and observation (HR 0.93, 95% CI: 0.84–1.04) (Figure S7). However, T-12 months, T-6 months and T-9 weeks were associated with significantly improved DFS compared to observation for lymph node-negative early breast cancer (Figure S7). Additionally, the results of the sensitivity analyses after excluding the trials that respectively reported 1–3 and >3 positive nodes remained essentially the same (Figure S7).

Subgroup and sensitivity analyses were also performed in hormone receptor-positive and hormone receptor-negative early breast cancer (Figure S8). T-24 months, T-12 months



**Figure 3** Pooled hazard ratios for disease-free survival (A) and overall survival (B) by network meta-analysis and pairwise meta-analysis. \*, doxorubicin and cyclophosphamide, followed by docetaxel plus trastuzumab (AC-TH); #, docetaxel and carboplatin, given concurrently with trastuzumab, followed by trastuzumab (TCH). CI, confidence interval for pairwise meta-analysis and the credible interval for NMA; NMA, network meta-analysis.



A	Observation	0.83 (0.81–0.86)	0.87 (0.83–0.91)	0.89 (0.84–0.93)	0.94 (0.76–1.17)	0.91 (0.84–0.98)
	T-12 months		1.03 (0.99–1.08)	1.06 (1.02–1.08)	1.13 (0.90–1.40)	1.08 (1.01–1.16)
			T-24 months	1.02 (0.96–1.09)	1.09 (0.88–1.36)	1.05 (0.96–1.13)
				T-6 months	1.06 (0.86–1.33)	1.02 (0.94–1.11)
					T-12 weeks	0.95 (0.75–1.19)
						T-9 weeks
B	Observation	0.87 (0.85–0.91)	0.88 (0.84–0.93)	0.93 (0.87–1.00)	1.01 (0.76–1.33)	0.94 (0.84–1.04)
	T-12 months		1.01 (0.96–1.06)	1.06 (1.00–1.13)	1.15 (0.87–1.51)	1.07 (0.97–1.18)
			T-24 months	1.05 (0.97–1.13)	1.14 (0.86–1.50)	1.06 (0.95–1.18)
				T-6 months	1.08 (0.82–1.43)	1.01 (0.90–1.13)
					T-12 weeks	0.91 (0.02–2.61)
						T-9 weeks

**Figure 4** Pooled hazard ratios for disease-free survival (A) and overall survival (B). The columns were compared with the rows. Numbers in parentheses represent the 95% CI. HRs with P values of less than 0.05 were considered statistically significant (red). T, trastuzumab.

and T-6 months were associated with significantly improved DFS than observation regardless of the hormone receptor status. However, T-9 weeks might be better than T-12 months and T-6 months. There were no differences among T-9 weeks, T-12 months, and T-6 months in the sensitivity analyses.

### Probability of efficacy and toxicity

All 16 trials included in this NMA reported information about congestive heart failure. In addition, data on acceptability, asymptomatic decline in the left ventricular ejection fraction and grade 3–4 nonhematologic toxicities were available in 15, 13 and 14 studies, respectively. The SUCRA findings showed that the ranking for the optimum duration of trastuzumab treatments with the best average probability of PFS was as follows: T-12 months (95.6%), T-24 months (69.6%), T-6 months (53.2%), T-9 weeks (41.2%), T-12 weeks (34.3%) and observation (6.1%) (Figure 5A). Similar SUCRA results were found for OS; here, T-12 months was the most effective (86.7%) treatment duration (Figure 5B).

T-24 months showed the worst effect in terms of elevated risk of trastuzumab-induced cardiotoxicity, with a mean probability of 83.6% for an asymptomatic decline in the left ventricular ejection fraction and 94.0% for congestive heart failure (Figure 5C,D). In addition, T-24 months conferred the greatest risk of grade 3–4 nonhematologic toxicities

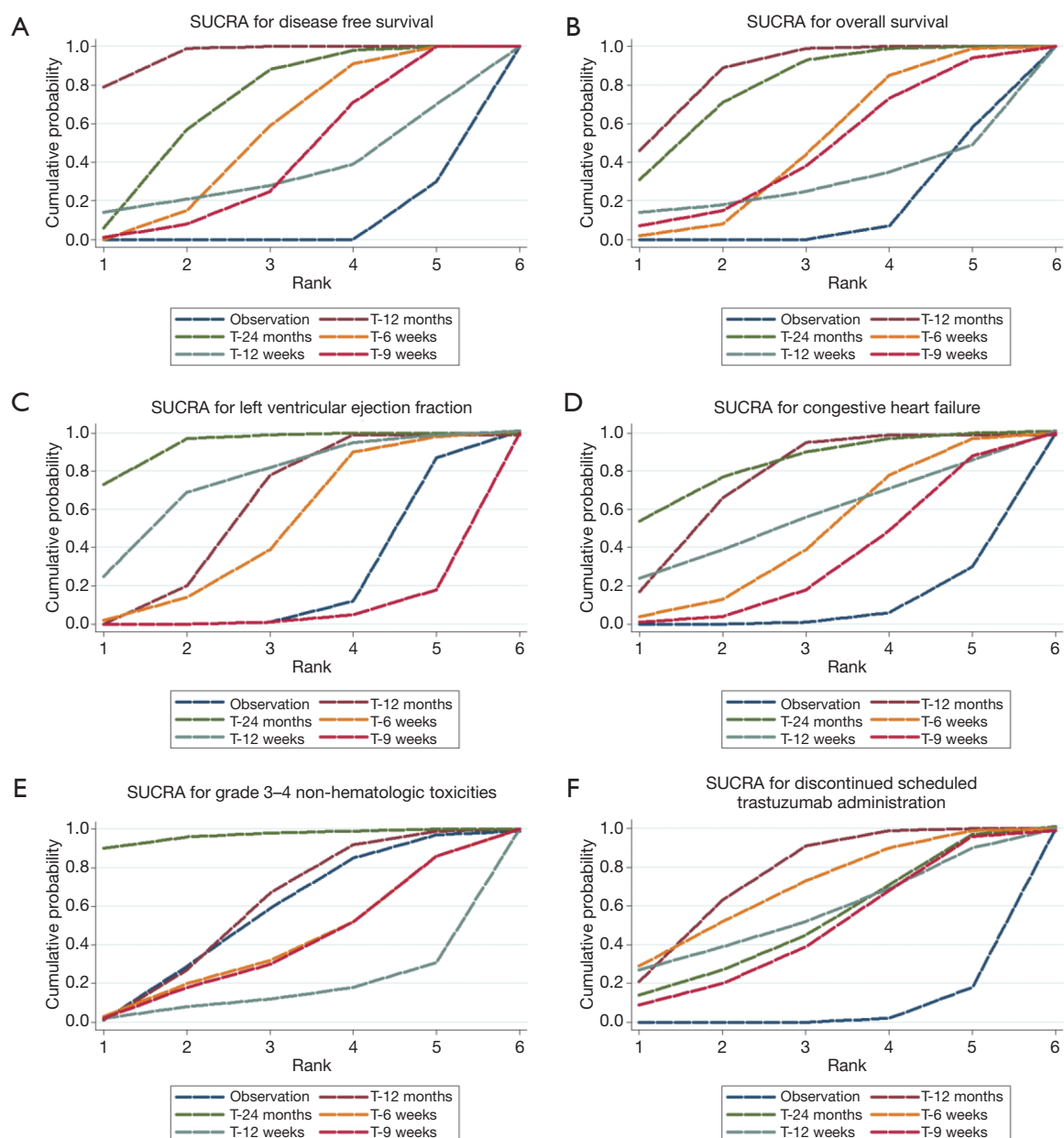
(SUCRA: 95.8%) (Figure 5E). Interestingly, T-12 months had the most frequent discontinued scheduled trastuzumab administration (SUCRA: 75%) (Figure 5F).

### Risk-benefit analyses

In our final analyses, we assessed the risk-benefit trade-offs between the relative treatment effects (PFS and OS) and cardiotoxicity (congestive heart failure). Here, we used the SUCRA values to calculate the risk-benefit ratios. Then, based on the risk-benefit ratios, we could divide the duration of adjuvant trastuzumab treatments into four broad categories: (I) T-12 months and T-24 months; (II) T-6 months and T-12 weeks; (III) T-9 weeks; (IV) Observation. We found that both T-12 months and T-24 months were associated with significantly improved DFS and OS, but they both caused more congestive heart failure events than de-escalating treatments (Figure 6). In summary, T-12 months and T-24 months were more effective in terms of improving survival than shorter treatments but caused more cardiotoxicity.

### Discussion

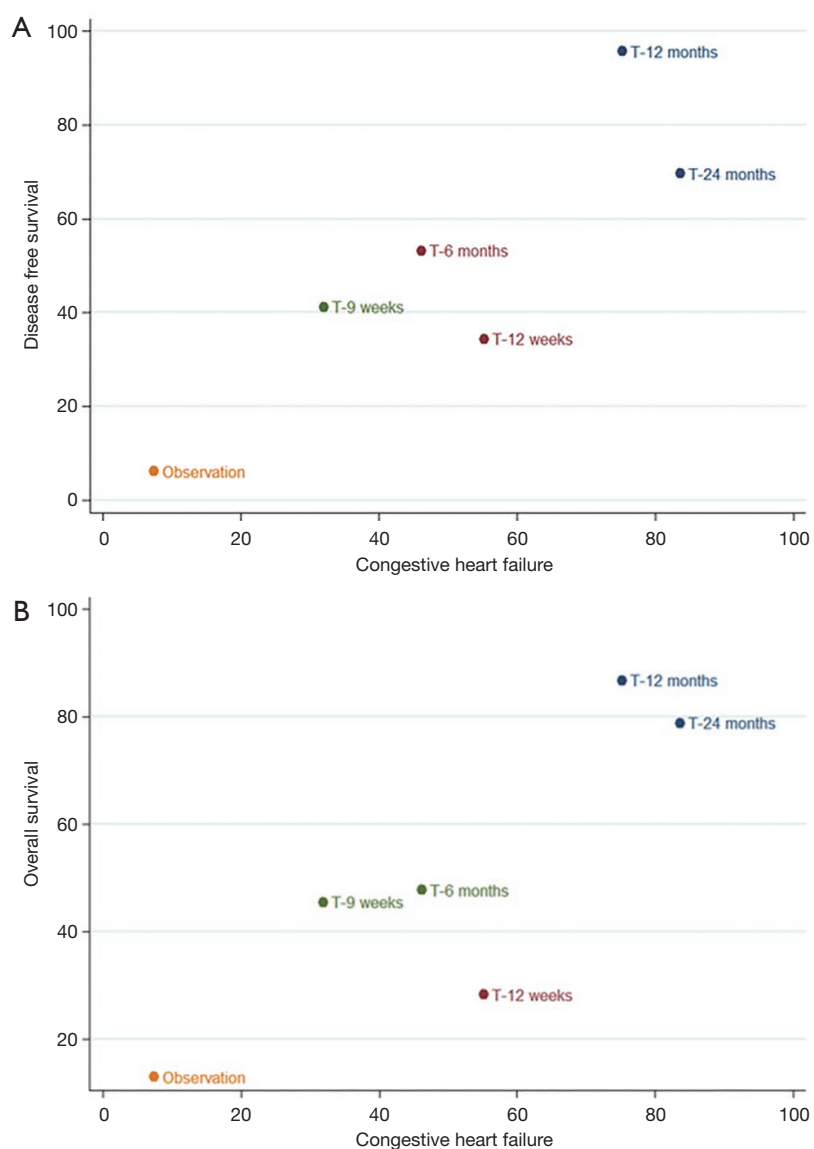
This NMA compared all major durations of adjuvant trastuzumab for HER2-positive early breast cancer and synthesized the available effects and safety of standard care, escalating and de-escalating treatments. Our results



**Figure 5** SUCRA values for the efficacy and trastuzumab tolerability in the NMA. SUCRA values for disease free survival (A), overall survival (B), left ventricular ejection fraction (C), congestive heart failure (D), grade 3–4 non-hematologic toxicities (E) and discontinued scheduled trastuzumab administration (F). The highest SUCRA value appeared at a depth of 100%, and the lowest value was close to zero. SUCRA, surface under the cumulative ranking; T, trastuzumab.

confirm that trastuzumab treatment for 12 months (T-12 months) is associated with a DFS and OS advantage over observation. Compared with T-12 months, escalating treatment (T-24 months) seems to provide no additional survival benefit but an increased risk of cardiac and grade 3–4 nonhematologic toxicities. T-6 months and T-9 weeks

seem to provide a significant DFS advantage, as shown in the indirect comparisons to observation; additionally, T-6 months is associated with a significantly improved DFS compared to T-12 months. No such significance was found when comparing T-9 weeks and T-12 months in NMA. We found no benefit of de-escalating treatment was statistically



**Figure 6** A risk-benefit analysis of congestive heart failure versus disease free survival or overall survival. SUCRA values for heart failure, disease free survival (A) or overall survival (B) were used to calculate the risk-benefit ratios in the NMA. The duration of adjuvant trastuzumab was divided into four broad categories according to the risk-benefit ratio. T, trastuzumab; SUCRA, surface under the cumulative ranking.

insignificant on OS in both the direct and indirect comparisons.

In agreement with our findings, earlier, traditional meta-analyses showed that 12-month trastuzumab treatment improves DFS and OS in patients with HER2-positive early breast cancer but confers an increased risk of cardiotoxicity than shorter treatment protocols (12,14-17). Our study offered that both T-12 months and T-24 months were associated with significantly improved DFS and OS,

but they both caused more congestive heart failure events than de-escalating treatments. The longer the use of trastuzumab, the higher the risk of trastuzumab induced cardiotoxicity. Selected patients, such as patients with a low risk of recurrence and with cardiac disease, might, therefore, be candidates for de-escalating treatments (15,16). Previous studies also showed that T12-month trastuzumab treatment prevents disease recurrence and confers survival benefits for patients with HER2-positive early breast

cancer compared with observation (55,56). These previous meta-analyses, however, were limited to two durations of trastuzumab treatment: shorter (T-6 months, T-12 weeks, and T-9 weeks) or standard treatment. Our study thus adds to these meta-analyses by also assessing the effects of escalating treatment. In addition, we provide data on effectiveness and safety by making direct comparisons and indirect comparisons. We also grouped the de-escalating treatments into three categories, T-6 months, T-12 weeks, or T-9 weeks, and compared these durations with each by Bayesian analysis.

Our findings suggest that the benefits of standard care (T-12 months) compared to T-6 months (HR 1.15, 95% CI: 1.01–1.28) and T-9 weeks were not associated with a DFS advantage in the direct comparisons (HR 1.25, 95% CI: 1.00–1.50). By contrast, a previous sensitivity analysis in a traditional meta-analysis according to the duration of trastuzumab treatments found a trend favoring T-12 months compared to both T-6 months (HR 1.18, 95% CI: 1.00–1.39) and T-9 weeks (HR 1.21, 95% CI: 1.06–1.53) (12). These results are inconsistent with those of our direct comparisons, due in part to the updated data included in our study. Our indirect results suggest that T-12 months provides a significant DFS advantage compared to either T-6 months (HR 1.06, 95% CI: 1.02–1.08) or T-9 weeks (HR 1.08, 95% CI: 1.01–1.16) in patients with HER2-positive early breast cancer. We also found by indirect analysis that T-6 months (HR 1.06, 95% CI: 1.02–1.08) and T-9 weeks (HR 1.08, 95% CI: 1.01–1.16) seem to be better DFS than observation. Based on these findings, de-escalating treatments might be a new choice for HER2-positive early breast cancer.

Our study is the first NMA, to the best of our knowledge, to compare the DFS of six interventions in subgroup and sensitivity analyses according to the lymph node and hormone status and among patients who received adjuvant and neoadjuvant treatments. The findings of our pairwise meta-analyses were consistent with the NMA, regardless of lymph node positivity or negativity. The pooled analysis suggests that T-12 months treatment confers a significant benefit in terms of DFS compared to observation, while we detected no significant benefit for de-escalating or standard treatments in the subgroup analysis. We also found that patients with lymph node negativity showed notable benefits from T-6 months and T-9 weeks treatment. A sensitivity analysis, however, revealed that there was a trend favoring T-9 weeks treatment based on the number of positive lymph nodes ( $\geq 1$ , 1–3 and  $\geq 4$  positive nodes). These data suggest

that lymph node status might not be a biomarker for de-escalating treatments.

For hormone receptor status, we similarly found that T-12 months and T-24 months were associated with increased DFS compared with observation, regardless of the hormone receptor status. In addition, T-6 months and T-9 weeks showed significant benefits of DFS compared to observation in the hormone receptor-positive and hormone receptor-negative subgroup. By contrast, T-9 weeks provided a DFS advantage in hormone receptor-negative patients according to the subgroup analysis compared to T-12 months, but not be confirmed in the sensitivity analysis. The optimum duration of trastuzumab treatment in patients with HER2-positive early breast cancer is currently unknown. These data suggest, however, that even if the standard treatment time is not achievable (T-12 months), it is better to use adjuvant trastuzumab than to perform observation. De-escalating treatments might also be an appropriate treatment option in selected patients, such as hormone receptor-negative patients. However, our results need to be confirmed with additional studies.

Some limitations of our NMA should be noted. Our review did not clarify the role of chemotherapy, lapatinib or pertuzumab for all trastuzumab treatment durations. However, a previous NMA detected a statistically significant difference in all approved trastuzumab-containing chemotherapies (57). This finding implies that clinical use of chemotherapy regimens combined with different trastuzumab durations show different benefits and harms for early-stage HER2-positive breast cancer. Future work should, therefore, combine chemotherapy protocols with anti-HER2 treatment times in the NMA. Furthermore, we also included patients with neoadjuvant trastuzumab-containing chemotherapy, whose clinical efficacy might be affected by tumor stage, as most patients had locally advanced breast cancer. In our study, we found that lymph node status might not be a good marker for de-escalating treatments in subgroup analysis based on lymph node status. Finally, this NMA had some missing patient information in the published data; thus, the cardiac events and grade 3–4 nonhematologic toxicities might be lower than those in clinical practice and might have affected the rank and risk-benefit assessment of efficacy and toxicity.

## Conclusions

In conclusion, the results of our NMA clearly show that T-12 months is the best standard-of-care for HER2-positive

early breast cancers. The unanswered question arises as to identify low risk patients with HER2-positive early breast cancer suited for de-escalating regimens of chemotherapy with trastuzumab durations. Importantly, our data support that if treatment does not reach the standard treatment time, it is better to use adjuvant trastuzumab than to perform observation. While de-escalating treatments confer only a small improvement in DFS in indirect comparisons, shorter treatment durations might be an appropriate choice for patients with hormone receptor- negative.

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## Footnote

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